DPP-4 INHIBITOR THERAPY AND BONE FRACTURES IN PEOPLE WITH TYPE 2 DIABETES – A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Aim Fracture risk is higher in older adults with Type 2 diabetes mellitus (T2DM). Oral glucose-lowering medications have different effects on bone metabolism. The purpose of this study is to appraise the evidence from literature and determine the effect of dipeptidyl peptidase-4 (DPP-4) inhibitor on the risk of developing bone fractures.

Methods Using Boolean search terms, the search strategy combined synonyms of 'fracture' and 'DPP-4 inhibitor'. Comprehensive electronic databases which include EMBASE, MEDLINE, the EMA and the WHO ICTRP databases were searched for randomised controlled trial (RCT) studies which compared a DPP-4 inhibitor with an active comparator or placebo amongst patients with T2DM. Meta-analysis was performed to compare DPP-4 inhibitor with either an active comparator or a placebo. The outcome measure was the presence or absence of fracture.

Results The search yielded 5,061 records relating to fractures and DPP-4 inhibitor, from which 51 eligible RCTs were selected for meta-analysis (N=36,402). Thirty-seven (37) studies compared DPP-4 inhibitor with placebo (n=23,974), while fourteen (14) studies (n=12,428) compared DPP-4 inhibitor with an active comparator. The mean age of patients was 57.5±5.4 years, the average glycated haemoglobin (HbA1c) was 8.2%, while the average BMI was 30±2 kg/m^2. Overall, there was no significant association of fracture events with the use of DPP-4 inhibitor when compared with placebo (OR; 0.82, 95%CI 0.57-1.16, P = 0.9) or when DPP-4 inhibitor was compared against an active comparator (OR; 1.59, 95% CI 0.91-2.80, P=0.9).

Conclusion This study offers a larger, up-to-date review of the subject. The meta-analysis showed that there was no significant association between DPP-4 inhibitor use and the incidence of fractures.

1. Introduction

Patients with type 2 diabetes mellitus (T2DM) are associated with an increased risk of developing bone fractures[1,2]. This is related to a variety of factors, such as recurrent falls[3] due to diabetes-related co-morbidities such as retinopathy, loss of balance, neuropathy and hypoglycaemic events[1,4,5] as well as hyperglycaemia induced alterations in tissue/matrix composition leading to osteoporosis and bone fragility[5]. Glucose-lowering therapy (GLT) such as thiazolidinedione has been reported to reduce bone density[6,7] and increase the risk of fractures.[8,9] In addition, Insulin therapy is also associated with an increased fracture risk,[10-12] despite its neutral effect on bone density.[13]

Experimental studies suggest that the incretin hormone glucagon like peptide-1 (GLP-1) and the gastric intestinal polypeptide (GIP) is capable of increasing bone density in animal models.[14,15] GLP-1 has also been reported to induce osteoblast differentiation and inhibits osteoclast activity[14,15]. DPP-4 inhibitors is a widely used GLTs that inhibits the breakdown of these incretin hormones and therefore induce a rise in the level of these incretin hormones and may exert protective effects on the bone[16]. Although bone mass density (BMD) has been shown to predict fracture incidence, BMD does not necessarily give a full picture of bone quality and strength.[5] For example, a meta-analysis of over 65 studies showed that BMD was decreased in patients with Type 1 diabetes mellitus, but increased in those with T2DM.[17] However, despite this higher than normal BMD, patients with T2DM remains at an increased risk of fractures, by around 20% in both sexes.[18]

A recent review and meta-analysis of RCT studies suggests that treatment with DPP-4 inhibitors could be associated with a reduced risk of bone fractures.[19] Monami et al., indicated that DPP-4 inhibitors, when compared with placebo or comparator treatments, were associated with fewer fracture events. The basis for this association may be explained by the

protective effect of DPP-4 inhibitors on the bone. In a 2014 animal model study,[20] the use of sitaglitpin (a DPP-4 inhibitor) in diabetic male rats increased trabecular bone volume, cortical bone volume and BMD. The loss of bone strength was attenuated, and bone biomarkers indicated a decrease in bone resorption. These findings are also supported by another study,[21] where high-fat diet-fed mice treated with sitagliptin showed an increase in vertebral BMD.

At the time of previous systematic reviews, there was scarce research directly investigating the effect of DPP-4 inhibitors on fracture incidence. Fractures were often noted as adverse events, rather than primary endpoints. Other oral GLTs reduce glycated haemoglobin (HbA1c), however, they have not been shown to have the same protective effect on bone as DPP-4 inhibitors. Thus, factor independent of glycaemic control may influence fracture risk. Due to limitations of the previous review, which are later discussed in this study, it is necessary to undertake an updated systematic review and meta-analysis. This is especially considering that since the 2011 meta-analysis,[19] a number of new robust RCTs investigating DPP-4 inhibitors have been published. The purpose of this study is to obtain an updated review and meta-analysis of the literature, to identify if DPP-4 inhibitors are associated with a decreased risk of bone fractures. Therefore, it is hypothesised that DPP-4 inhibitors will have a protective effect against fractures, as already demonstrated in an earlier review.[19]

2. Methods

2.1 Data sources and search strategy

A series of searches were performed, investigating the association between fracture incidence and the use of DPP-4 inhibitors in patients with T2DM. Comprehensive electronic databases were searched. Using Boolean search terms, the search strategy combined synonyms of ‘fracture’ and ‘DPP-4 inhibitor’. The data sources include EMBASE (1974-2015) and MEDLINE (1946-2015). Reviews of approved drugs were identified manually on the

European Medicines Agency (EMA) database. WHO International Clinical Trials Registry Platform (ICTRP), including clinicaltrials.gov, was searched to identify clinical trials. There was also manual searching of the supplementary data within the Monami et al., 2011 study.[19]

2.2 Study selection and eligibility

The preferred reporting items for systematic reviews and meta-analyses (PRISMA) 2009 checklist was used to structure the method of the review.

The studies were assessed first by their titles, then by the abstract and followed by full text review. Titles and abstracts that were included mentioned synonyms for DPP-4 inhibitors, and the patient group with T2DM. Titles and abstract contradicting the search terms, by mentioning the wrong intervention, and conditions that were not T2DM were excluded. Within the clinicaltrials.gov searches, only the titles with the recruitment statuses, 'not recruiting' and 'authorised' were selected. Studies that were 'not yet recruiting', unfinished studies and studies without any data published were excluded. The relevant articles were assessed according to eligibility criteria.

The aim of the search was to identify RCTs that compared the intervention with a comparator drug or placebo, amongst T2DM patients. Therefore, only RCTs were used as these are higher quality studies with better control and replicability. The intervention had to be either a DPP-4 inhibitor, and the outcome measure recorded was the number of fractures. The studies were manually searched for the term, 'fracture' to identify if fractures had occurred during the trial. If this was not present, then the study would be excluded. Non-English articles were not included. Only human studies were used, as these were the most relevant to application of results to patients with T2DM. There was no restriction on the publication date of articles, as all studies up until June, 2015 were included.

2.3 Data abstraction

The data of interest were the number of fracture events during the trials. A data extraction form was utilised to record different characteristics of each study; including the author, year of publication, clinical trial number, the duration of the trial (weeks), the intervention and comparator used, the number of participants in each group, sex (% of females), the mean age, the mean baseline HbA1c (%), mean baseline BMI (kg/m^2), hypoglycaemic events (% of participants), and the number of fractures in both the intervention and the comparator groups.

2.4 Data synthesis and analysis

Eligible studies that were used in the meta-analysis were based on whether they included a DPP-4 inhibitor treatment, in addition to an active comparator or placebo treatment. Studies were also included that involved combination therapy within the intervention, active comparator or placebo arms.

2.5 Meta-analysis

Meta-analysis was conducted to assess and determine whether the use of DPP-4 inhibitor in the treatment of T2DM has a causal contribution to the development of bone fracture. Meta-analysis was used to calculate the average measure of effect by assembling quantitative results from several RCT studies together. The number of fracture events reported in the exposed and unexposed (comparator) treatment groups of each primary study was extracted and used to calculate a new single measure of effect (pooled result or summary statistic). The pooled data from the studies were expressed as odds ratio, together with their precision (95% confidence interval). The results from all of the studies were summarized and displayed using forest plots.

2.5.1 Assessing heterogeneity between studies

Analysis was conducted to assess the similarity of results from each of the studies. The term heterogeneity was used to describe the degree to which the studies varied. The I^2 statistical test was used to quantify the effect of heterogeneity between the results of the studies. I^2 value range from 0% to 100%, representing the percentage of total variation across the studies that is due to true heterogeneity rather than to chance. A value of 0% would indicate that there is no variability between studies that cannot be explained by chance, whereas, a value of 50% would indicate that 50% of the total variability in the meta-analysis is due to heterogeneity rather than to chance, and a value of 100% would indicate that all of the variation in the meta-analysis is due to heterogeneity rather than to chance. I^2 by itself was not used to explain the actual range of effects[22] but was used together with the observed effects from the forest plots to get a sense of the absolute dispersion.

2.5.2 Pooling meta-analysis data

We considered the use of random effects model (where we assumed the true effect varied from study to study). We also considered the application of a fixed effects model (where we assumed that there was one true effect size shared by all the included RCT studies). The resulting I^2 value determined which effect model was more favourable. If the I^2 in the output is low (<40%), we would run the fixed effects model. The fixed-effects method was eventually used to pool the effect estimates of the studies together to generate the summary statistic odds ratio. The fixed effect method calculates a weighted average of the odds ratio from all of the different studies – the weight being proportional to the size of the study. Therefore the bigger the sample size of a study, the more influence it has on the pooled odds ratio. The fixed effect method assumes that all of the available studies are trying to estimate the same true value.[23]

2.6 Bias assessment

The JADAD scale was used to assess the method and appropriateness of randomisation, blinding and follow-up of participants in each study.[24] A potential problem that can occur during the primary study search process is publication bias. This could occur when published studies that have found "interesting" (usually positive) results are more likely to be identified in during search and more likely to be published earlier than the "less interesting" (usually negative) ones. The extent of publication bias was assessed through the inspection of the magnitude of published effects in relation to the order of publication by year. In addition, funnel plots of the magnitude of the odds ratio against the study precision were used to assess the influence of publication bias.[25,26]

3. Results

The initial database searches identified 5,049 records relating to fractures and DPP-4 inhibitors. In addition to this, 12 studies were manually identified from a previous meta-analysis.[19] From these, 51 studies met the criteria for inclusion in the meta-analysis as outlined in Figure 3.1. The patient characteristics of the eligible studies are summarised in Tables 3.1 and Table 3.2.

3.1 Study characteristics

The searches resulted in 51 RCTs with 36,402 participants. Thirty-seven (37) studies compared a DPP-4 inhibitor with a placebo, involving 23,974 patients. Fourteen (14) studies including 12,428 patients were used in the comparison of a DPP-4 inhibitor against an active comparator. The mean (standard deviation, SD) age of patients was 57.5 (5.4) years and 47% of the entire population was female. Participants had a mean (SD) body mass index (BMI) of 30.2 (2.0) kg/m^2. The average HbA1c was 8.2% and the percentage of patients who

experienced a hypoglycaemic event was lower in the intervention compared to the comparator group (4.3% vs 5.3%, respectively).

There were 39 multi-country trials, nine multisite trials, and two trials in the US. The durations of the studies ranged from 12 to 205 weeks, with an average of 47.8 weeks. There were 29 RCTs with a duration < 52 weeks, and 22 studies were >52 weeks. The earliest dated study was in 2006,[27] with the most recent study being published in 2014.[28]

3.1.1 Intervention

The DPP-4 inhibitors investigated in each RCT are as follows: 5 studies with alogliptin, 3 with linagliptin, 12 studies with saxagliptin, 29 with sitagliptin and two studies with vildagliptin. Considering the placebo groups, a total of 28 studies (55%) had placebo in combination with another drug. Within the active comparator groups, five studies (35%) were combination therapies.[29-33] Eight studies involved the use of metformin, and another eight studies involved the use of a sulfonylurea. Two studies included a thiazolidinedione,[33,34] while one study included a glucagon-like peptide-1 (GLP-1) receptor agonists[31] and one study involved voglibose, an alpha-glucosidase inhibitor (AGI).[35] Overall, there were 86 cases of fracture in the intervention group, and 64 cases with the comparators. The most common types of fracture recorded include lower limb (12 cases), followed by ankle (10 cases) and then rib (8 cases).

3.1.2 Outcomes

All studies had a primary outcome measure of HbA1c change from baseline. This is with the exception of Alba et al.,[36] who measured changes in α-cell and β-cell function; insulin secretion rate in the clinical trial study NCT00374907;[37] the percentage of individuals experiencing a primary major cardiac event (MACE) in NCT00968708;[38] and the proportion of patients under a HbA1c of 7.0% without any sings of severe hypoglycaemia, as measured

in NCT01006603.[39] The secondary outcomes were varied, but mostly included efficacy assessments such as change in glucose, insulin, proinsulin, fasting plasma glucose (FPG), 2-hour post-meal glucose (PMG), body weight and fasting lipids. Two studies included safety assessments such as blood pressure and cases of secondary MACE.[38,40]

3.1.3 RCT exclusion and inclusion criteria

Two authors participated in the literature search, while agreement on criteria for inclusion of RCTs was reached by consensus between 3 authors. The studies had mostly similar inclusion criteria, with no restrictions on the gender of the patient. Studies were restricted to patients with T2DM with inadequate glycaemic control either with diet and exercise alone. The mean range of requirements, inclusively were an HbA1c level from 7 to 10%; a BMI between 22 to 43kg/m^2; and age 22 to 78 years. Eleven studies required the patients to be unlikely to conceive, or to use contraception. Two studies set limitations for blood pressure (BP),[41,42] only including participants with a BP up to 170/105mmHg. On average, three studies required patients to have had diabetes duration for a minimum of 2 years.[36,43,44] Four studies included patients with renal impairment.[45-48] One study,[38] used patients with acute coronary syndrome between 15 and 90 days prior to the study. Two studies only included patients that would have the ability to use home blood glucose monitoring,[29,49] and one study included the patients able to use an injection device.[31]

Exclusion criteria differed across the study, but the most commonly encountered criteria were; a history of CV event; females who are pregnant or breastfeeding; patients that refused the use of contraception; the presence of hepatic and renal disease; secondary forms of diabetes; Type 1 diabetes mellitus; a history of diabetic ketoacidosis; symptoms of poorly controlled diabetes; recent gastrointestinal surgery; the prior use of a weight loss drug treatment; the use of any other hyperglycaemic agents; alcohol and substance use; hypersensitivity to any of the treatments; and uncontrolled hypertension.

3.2 Meta-analysis

3.2.1 DPP-4 inhibitor and fracture incidence

Statistical analysis was carried out in order to investigate the association of fractures with the use of DPP-4 inhibitors. The primary outcome was the number of fracture events. From these, the odds ratio (OR) was calculated. Two subgroup analyses were performed, comparing the incidence of fractures with DPP-4 inhibitors; and active comparators or a placebo. Overall there was no significant association of fracture events with the use of DPP-4 inhibitors.

3.2.2 DPP-4 inhibitor vs placebo

A subgroup analysis comparing DPP-4 inhibitors to placebo is displayed by the forest plot in Figure 3.2. The I^2 value obtained was equal to 0.0%, indicating no presence of heterogeneity. Results from the fixed effect model analysis gave a non-significant P value of 0.9. The OR was 0.82 with a 95% CI of 0.57-1.16.

3.2.3 DPP-4 inhibitor vs active comparator

A subgroup analysis on DPP-4 inhibitors compared with an active comparator is displayed by the forest plot in Figure 3.3. The I^2 value was equal to 0.0%, indicating homogeneity. The OR of 1.59 with a 95%CI of 0.91-2.80 (P value, 0.9) was obtained from the fixed effect model.

3.3 Bias assessment

3.3.1 Quality assessment

The JADAD scale was used to assess the quality of each study. Thirteen (13) studies obtained a score of 5, thirty one (31) studies obtained a score of 4, while seven (7) studies obtained a score of 3, with no study obtaining a score below 3. The average score was 4, therefore the overall quality of RCTs was good.

3.3.2 Randomisation and blinding

All studies were randomised, with 9 studies being randomised by computer generated allocation. 36 studies did not mention the method used for randomisation. 7 studies were stratified according to certain factors. Forty three of the studies were double-blind with a matching placebo. Seven studies did not use a placebo, and one study was open label.[31]

3.3.3 Publication bias

The effect of publication bias was reduced by ensuring that the systematic review of published literature was as thorough as possible. Additional hand searching of references quoted by each paper was done to make sure all relevant literature was found. Unpublished data were also obtained and included, which may reduce publication bias, although this may also decrease validity as unpublished work has not been peer reviewed. The funnel plots presented in Supplementary Figures 1 and 2 show the funnels are approximately symmetrical, indicating the absence of publication bias.

4. Discussion

This systematic review and meta-analysis studied the effect of DPP-4 inhibitors on fracture incidence in T2DM. The meta-analysis of 51 RCTs showed that there was no significant association between DPP-4 inhibitor use and the occurrence of fractures when DPP-4 inhibitor is compared with placebo or active comparator.

From the quality assessments, it can be concluded that the RCT studies were well-designed, giving rise to evidence of a good strength. The forest plots and I^2 values of 0.0% in both meta-analyses indicated that there was no statistical heterogeneity. This means that any variability across the studies could be attributable to chance, not to the heterogeneity of the studies themselves.[50] This consistency amongst studies should provide a confidence in applying these results.[51] Therefore, results from this meta-analysis can be considered to have

a good level of internal validity. In addition, the large sample size and multinational representation reflects this study's external validity.

In the context of the research surrounding the role of incretin hormones in bone metabolism, this study demonstrates no significant reduction of fracture incidence with the use of DPP-4 inhibitors. This is in contrast to Monami et al.,[19] who displayed that there was a statistically significant association between DPP-4 inhibitor use and reduced occurrence of fracture. From Monami et al study, 17 of the 20 trials comparing DPP-4 inhibitors with placebo were used in this meta-analysis. Three trials were not included, since these did not mention that a fracture event occurred during the study.[52-54] There was also no mention that authors of the original studies were contacted for this information. The limitations associated with the review by Monami et al emphasised the necessity of an updated meta-analysis comprising of a greater number of patient data. Furthermore, this meta-analysis included 22 trials with study duration of 52 weeks and above, whereas the previous review included only 7 trials with ≥52 weeks.[19]

Another meta-analysis of RCT studies by Su et al[55] examined the risk of bone fractures associated with GLP-1 receptor agonists (liraglutide and exenatide) when compared with placebo or active comparator treatment. Incident fracture data from 11,206 patients was pooled across 16 RCTs and the results showed treatment with liraglutide was associated with a significant reduction in the risk of bone fracture (MH-OR: 0.38, 95% CI: 0.17–0.87), while treatment with exenatide was associated with an increased risk of bone fractures (MH-OR: 2.09, 95% CI: 1.03–4.21).

The contrasting results that have emerged from these incretin-based therapy review studies show the need for further investigations into the role of incretin hormones in bone metabolism across various populations. The reason for this disparity between results from previous reviews and this current review study cannot be explained from our data. However,

we assume that other underlying factors such as lifestyle changes might play a significant role. The disparity in the results obtained from previous reviews of RCTs implies that that a definitive conclusion cannot be made on the effect of DPP-4 inhibitor on bone fractures in the long-term.

The SAVOR-TIMI 53 study by Scirca et al.,[56] was conducted across 16,492 T2DM patients for a median of 2.1 years. This large, multisite, double-blind RCT investigated cardiovascular outcomes in T2D patients, comparing the effects of saxagliptin with placebo. In keeping with this meta-analysis, it was found that there was no significant difference in the number of patients experiencing a fracture, between the saxagliptin and placebo group (P = 1.0). In addition, a large-scale retrospective cohort study by Driessen et al.,[57] directly investigated the effect of DPP-4 inhibitor use on fracture risk. Information from the Clinical Practice Research Datalink (CPRD) database on 216,816 patients was examined. The study demonstrated no significant difference in the hazard risk of fractures, between DPP-4 inhibitor users and matched control patients (adjusted hazard ratio 0.89; 95% CI of 0.71-1.13).

The studies included in our review are not without their limitations. For example, RCTs had an average duration or follow-up of 37.5 weeks. This may be too short of a follow-up time to observe fracture events. In addition to this, fracture was not reported as a primary end-point in any of the studies, but only as an adverse event.

As in the previous review,[19] combination therapy was also included within the intervention, active comparator and placebo arms. As a result, the inclusion of these combination therapies may have exerted an effect on the outcome (the number of fractures). In future, a meta-regression could be performed, in order to identify the significance of this effect.

Nonetheless, the presence of combination therapies in many patients accurately reflects the reality that single drug therapy is often insufficient to control glycaemic levels.

Another limitation of this review was the unavailability of some data, especially within unpublished, yet disclosed trials from the clinicaltrials.gov website. If a published article referring to the same clinical trial identifier number could be identified, missing data were obtained from that source. In the case that there was no published article for a clinical trial, or no additional information within the published article, data were marked as 'not reported' (NR). It is acknowledged that this missing data may have given an incomplete picture of patient characteristics. However, the data that were missing did not relate to the outcome measure of this review.

The use of RCTs provides a high level of internal validity, improving the strength of recommendation for the practice of evidence-based medicine. Still, RCTs may not have a high level of external validity. This is since they may not accurately reflect a real-world environment where factors are not so tightly controlled. However, these rigorous methods allow the conclusion to be made, that the difference in the outcome being measured, is in fact due to a change in the independent variable. This systematic review has demonstrated the absence of a significant association between DPP-4 inhibitor and fracture incidence.

While DPP-4 inhibitors have not been shown to significantly protect against fracture, this research is still valuable in informing the choices of healthcare providers in prescribing treatments from this class of drugs. For the users of this treatment, it is good news that DPP-4 inhibitors are not generally associated with fracture incidence, in contrast to thiazolidinedione, which are known to be associated with increased fracture risk, or with exenatide, which was recently shown to be associated with increased risk of bone fracture.[55] The results drawn from RCTs in the field are varied, meaning that a definitive conclusion

cannot be made on the role of DPP-4 inhibitors in protecting against bone fractures. The results of this review imply that future research should include studies of a longer duration. In addition, more studies are required to directly investigate the number of fractures with the use of DPP-4 inhibitors, as a primary endpoint, rather than an adverse event.

TableRefs[27-47,49,58-83]

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Figure 3.1 Study screening

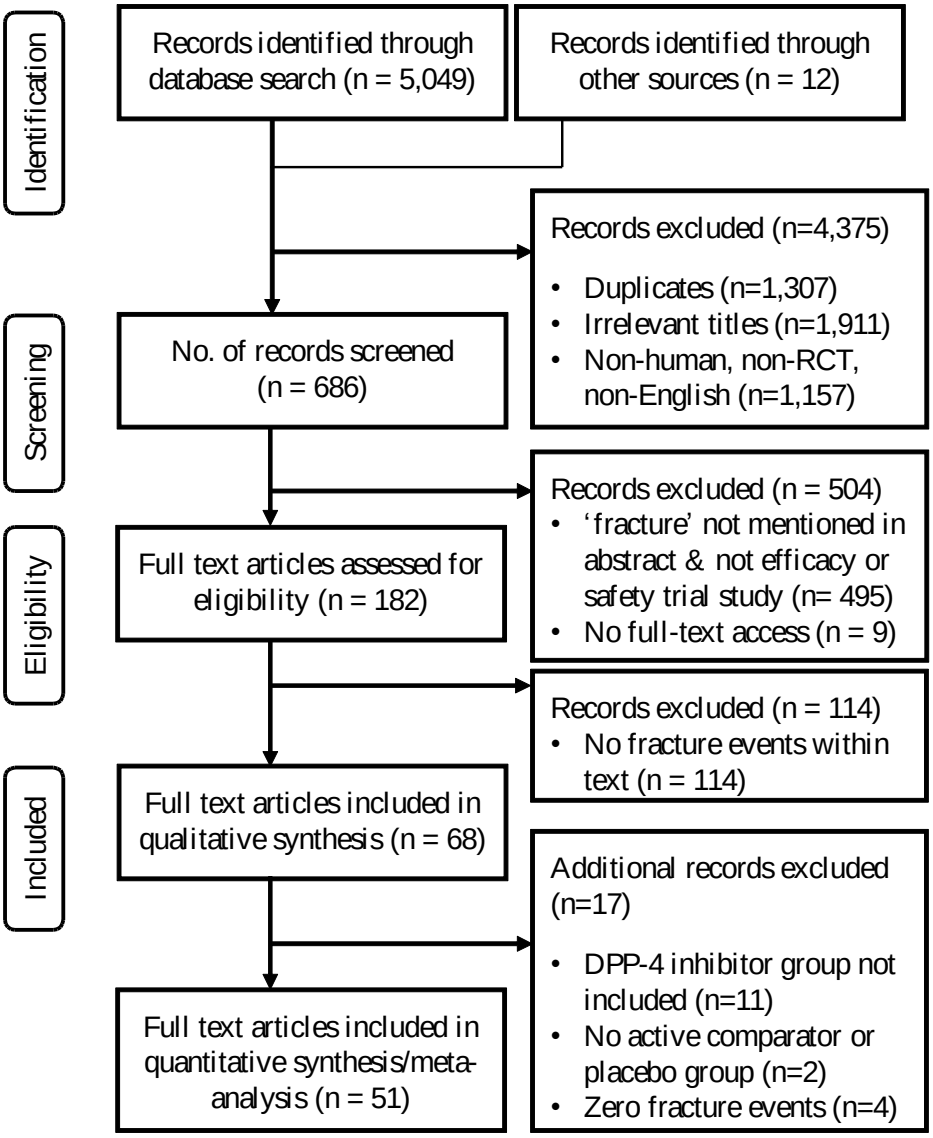

Figure 3.2 Forest plot of fracture cases among DPP-4 inhibitor vs. placebo

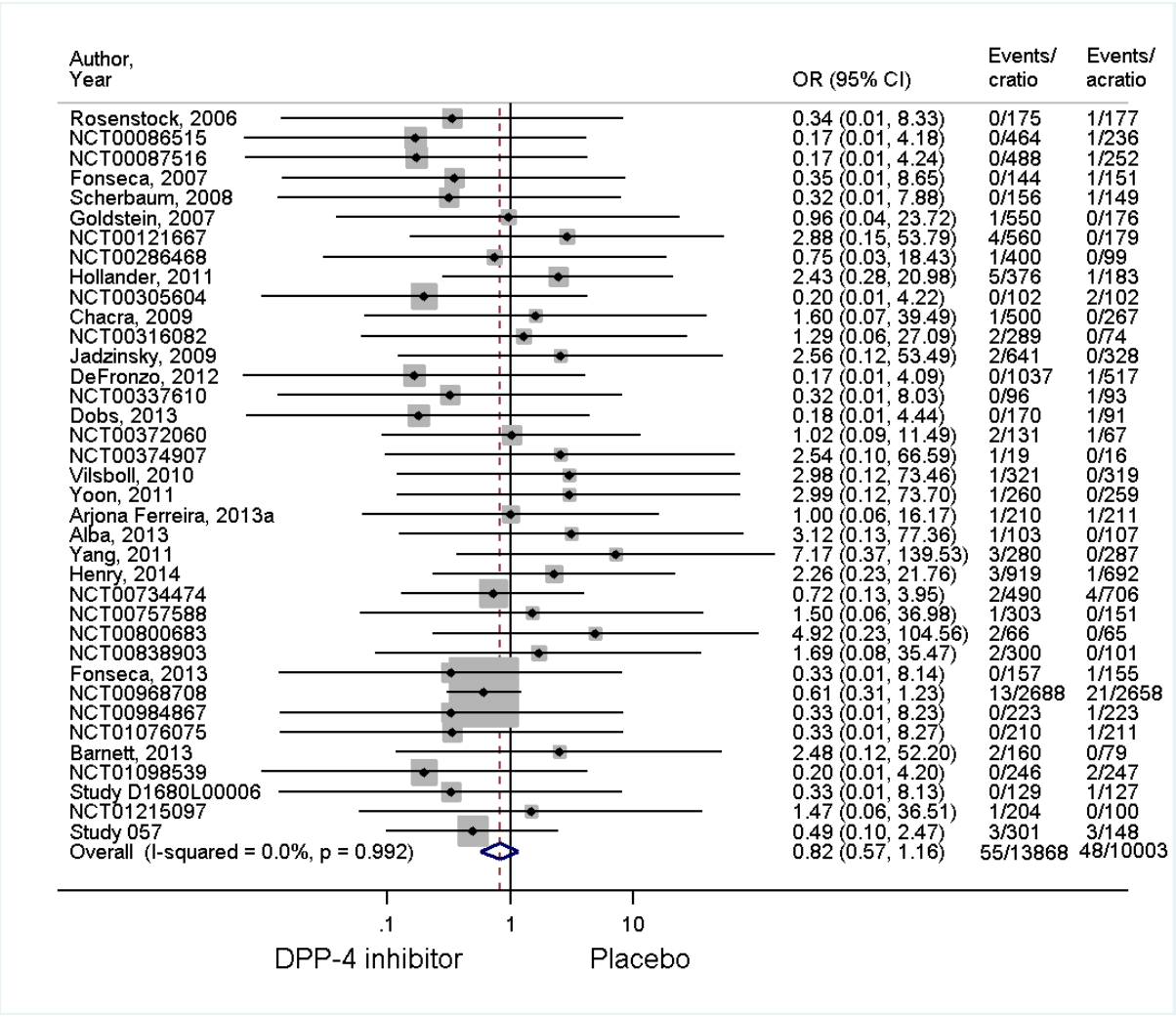

Figure 3.3 Forest plot for DPP-4 inhibitor vs. active comparator

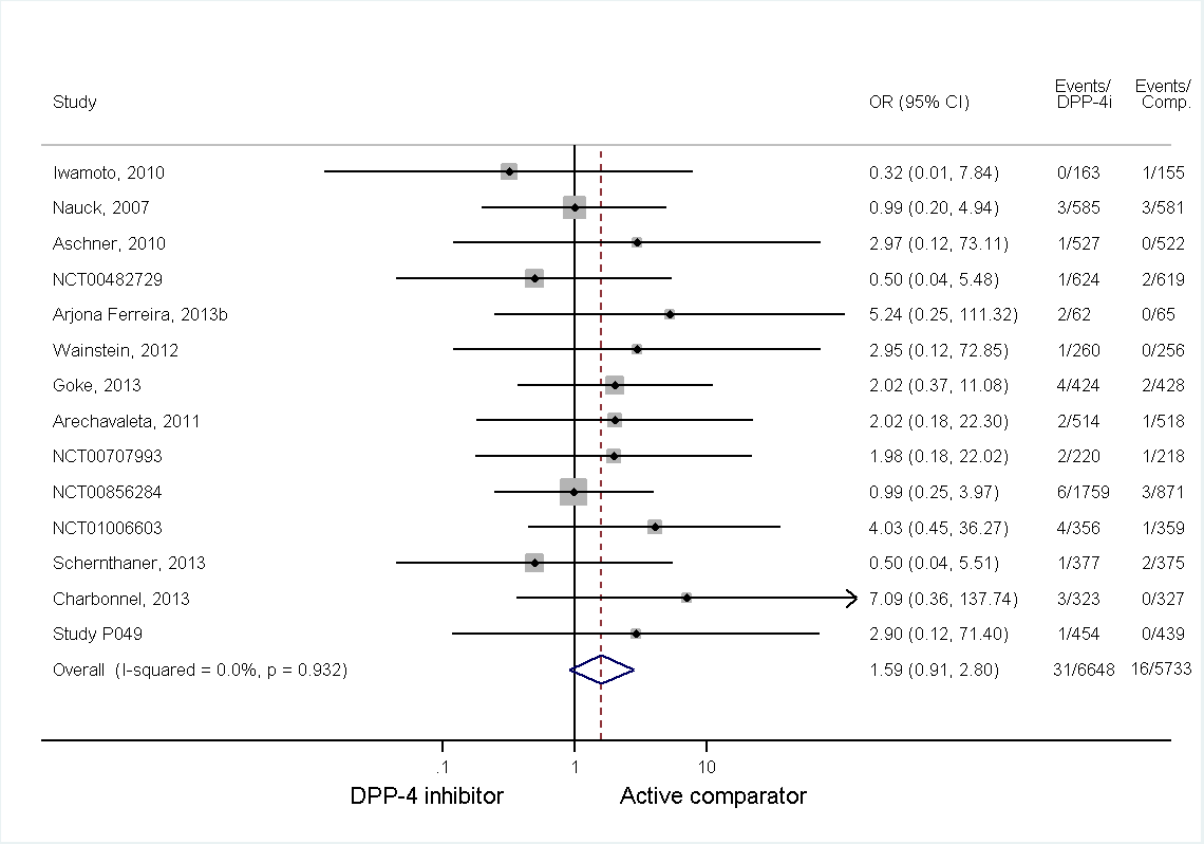

Table 3.1: Patient characteristics for RCT studies involving DPP-4 inhibitor and placebo

Author, Year	Clinical trial No.	population	F, %	Age, yrs	HbA1c, %	BMI	Wks	Intervention	n	No. of fractures	Comparator	n	No. of fractures
Hollander, 2011	NCT00295633	Multisite	51	54 (0.9)	8.3 (0.1)	30 (0.3)	76	Sitagliptin (2.5mg, 5mg)	381	5	Placebo/TZD	184	1
Yang, 2011	NCT00661362	Multisite in China, India, South Korea	52	54 (0.4)	7.9 (0)	26.2 (0.1)	24	Saxagliptin (5mg)	283	3	Placebo/Metformin	287	0
Scherbaum, 2008	NCT00101712	Multisite in Europe	41	63 (0.4)	6.8 (0.1)	30.2 (0.3)	52	Vildagliptin (50mg)	156	0	Placebo	150	1 cervical
Fonseca, 2007	NCT00099931	Multi-country	49	59 (0.5)	8.4 (1.1)	33.1 (5.6)	24	Vildagliptin (50mg) BID	144	0	Placebo/Insulin	152	1
NCT00286468	NCT00286468	Multi-country	48	57 (0.4)	8.1 (0)	30.1 (1.1)	26	Alogliptin (12.5mg, 25mg)	401	1 spinal compression	Placebo/Glyburide	99	0
Dobs, 2013	NCT00350779	Multi-country	42	55 (0.3)	8.8 (1)	30.3 (6)	54	Sitagliptin (100mg)	170	0	Placebo/Rosiglitazone/ Metformin	92	1 lower limb
NCT01076075	NCT01076075	NR	54	55 (0.7)	8.4 (0.8)	NR	54	Sitagliptin (100mg)	210	0	Placebo/Pioglitazone	212	1 skull
Barnett, 2013	NCT01084005	Multi-country	33	75 (0)	7.8 (0.1)	29.7 (0.1)	24	Linagliptin (5mg)	162	1 lower limb 1 vertebra	Placebo	79	0
NCT00316082	NCT00316082	Multi-country	54	55 (10)	7.9 (0.1)	NR	24	Saxagliptin (2.5mg, 5mg)	291	1 femoral neck 1 spinal	Placebo	74	0
Jadzinsky, 2009	NCT00327015	Multi-country	51	52 (11)	9.5 (0.1)	30.2 (4.8)	24	Saxagliptin (5mg, 10mg)	643	1 upper limb 1 wrist	Placebo/Metformin	328	0
Chacra, 2009	NCT00313313	Multi-country	55	55 (10)	8.4 (0.1)	29 (4.6)	24	Saxagliptin (2.5mg, 5mg)	501	1 lower limb	Placebo/Glyburide	267	0
NCT00305604	NCT00305604	US	35	72 (6)	7.8 (0.7)	NR	24	Sitagliptin (50mg/ 100mg)	102	0	Placebo	104	1 lumbar vertebra, 1 upper limb
Fonseca, 2013	NCT00885352	Multi-country	38	56 (9)	8.7 (1)	30 (5.2)	26	Sitagliptin (100mg)	157	0	Placebo	156	1 patella
NCT00121667	NCT00121667	Multi-country	49	55 (10)	8.1 (0.1)	31.4 (4.9)	24	Saxagliptin (2.5mg, 5mg, 10mg)	564	4	Placebo/Metformin /Pioglitazone	179	0
Goldstein, 2007	NCT00103857	Multi-country	50	53 (9.9)	9 (1.2)	32.1 (6.6)	24	Sitagliptin (50mg BID,	551	1 femur	Placebo/Metformin	176	0

Author, Year	Clinical trial No.	population	F, %	Age, yrs	HbA1c, %	BMI	Wks	Intervention	n	No. of fractures	Comparator	n	No. of fractures
								100mg QD)					
NCT00087516	NCT00087516	Multi-country	48	54 (9.9)	8 (0.9)	NR	24	Sitagliptin (100mg, 200mg)	488	0	Placebo	253	1 ankle
NCT00086515	NCT00086515	Multi-country	43	55 (10)	8 (0.8)	NR	104	Sitagliptin (100mg)	464	0	Placebo/Glipizide	237	1 traumatic
NCT01215097	NCT01215097	Multisite in China, Malaysia, Philippines	50	56 (10)	8 (0.8)	25.6 (4)	24	Linagliptin (5mg)	205	1 comminuted	Placebo	100	0
NCT00984867	NCT00984867	Multi-country	45	55 (10)	7.9 (0.8)	NR	24	Sitagliptin	223	0	Placebo/Sitagliptin/ Metformin	224	1 upper limb
NCT00968708	NCT00968708	Multi-country	32	61 (9.9)	NR	29.5 (5.6)	205	Alogliptin (6.25mg/ 12.5mg/ 25mg)	2701	13	Placebo	2679	21
NCT00757588	NCT00757588	Multi-country	59	57 (9.4)	NR	NR	24	Saxagliptin (5mg)	304	1 ankle	Placebo/Insulin	151	0
NCT00734474	NCT00734474	Multi-country	54	54 (9.9)	8.1 (1.1)	31.3 (4.4)	104	Sitagliptin (100mg)	492	2	Placebo/Dutaglutide /Metformin	710	4
NCT00800683	NCT00800683	Multi-country	40	64 (10)	8.2 (1)	32 (5.8)	52	Linagliptin (5mg)	68	1 femur 1 humerus	Placebo	65	0
Henry, 2014	NCT00722371	NR	44	52 (1.1)	8.8 (1.1)	30.9 (5.4)	54	Sitagliptin (100mg)	922	2 foot 1 upper limb	Placebo/ Pioglitazone	693	1 foot
Alba, 2013	NCT00511108	Multi-country	45	54 (7.9)	7.9 (1)	30.9 (4.8)	21	Sitagliptin (100mg)	104	1 tibia	Placebo/Pioglitazone	107	0
Yoon, 2011	NCT00397631	Multi-country	46	51 (11)	9.5 (1.2)	29.7 (5.2)	24	Sitagliptin (100mg)	261	1 humerus	Placebo/ Pioglitazone	259	0
Vilsboll, 2010	NCT00395343	Multi-country	49	58 (9.2)	8.7 (0.9)	31 (5)	24	Sitagliptin (100mg)	322	1 pelvic	Placebo/Insulin/ Metformin	319	0
NCT00374907	NCT00374907	US	61	57 (2.1)	NR	32.8 (0.7)	116	Saxgliptin (5mg)	20	1 ankle	Placebo/Metformin	16	0
NCT00372060	NCT00372060	Multisite in Japan	35	58 (9.5)	7.7 (0.8)	NR	52	Sitagliptin (50mg-100mg)	133	1 patella 1 rib	Placebo/Sitagliptin Pioglitazone	68	1 lower limb
NCT00337610	NCT00337610	Multi-country	54	55 (9.5)	9.2 (0.8)	NR	30	Sitagliptin (100mg)	96	0	Placebo/Metformin	94	1 upper limb
DeFronzo,2012	NCT00328627	Multi-country	55	54 (9.5)	8.5 (0.7)	31.2 (5.1)	26	Alogliptin (12.5mg, 25mg)	1037	0	Placebo/Pioglitazone	518	1 ankle
NCT00838903	NCT00838903	Multi-country	52	55 (10)	NR	NR	156	Sitagliptin (100mg)	302	1 femur 1 spinal	Placebo/Metformin	101	0

Author, Year	Clinical trial No.	population	F, %	Age, yrs	HbA1c, %	BMI	Wks	Intervention	n	No. of fractures	Comparator	n	No. of fractures
Study 057	NR	Multisite	59	57 (NR)	8.7 (0.9)	32.3 (NR)	52	Saxagliptin (5mg)	304	2 foot 1 ankle	Placebo/Insulin	151	1 hand, 1 humerus, 1 lower limb
Rosenstock, 2006	NCT00086502	Multi-country	45	56 (11)	8 (0.8)	31.5 (5.1)	24	Saxagliptin (100mg)	175	0	Placebo/Pioglitazone	178	1 lower limb
Study D1680L00006	NCT01128153	Multi-country	40	57 (11)	8.3 (0.8)	29.2 (5.1)	24	Saxagliptin (5mg)	129	0	Placebo/Metformin/ Sulfonylurea	128	1 rib
NCT01098539	NCT01098539	Multi-country	46	63 (8.7)	NR	NR	52	Sitagliptin (25mg-100mg)	246	0	Placebo/Albiglutide	249	1 radius, 1 sternal
Arjona Ferreira, 2013a	NCT00509262	Multi-country	40	64 (10)	7.8 (0.7)	26.8 (4.8)	54	Sitagliptin (25mg/ 50mg)	211	1 patella	Placebo/Glipizide	212	1 femur

Abbreviation: F (female); Wks (duration in weeks); n (sample size); BMI (body mass index in Kg/m^2); HbA1c (glycated haemoglobin); TZD (thiazolidinedione); NR (not reported);
Mean (standard deviation) reported for age, HbA1c and BMI.
The patients had a mean age of 57 years, ranging from 50.9 to 74.9 years. There were 48 cases of fracture amongst 10,051 patients in the placebo group, and 55 fractures amongst 13,923 patients taking a DPP-4 inhibitor

Table 3.2: Patient characteristics for RCT studies involving DPP-4 inhibitor and active comparator

Author, Year	Clinical trial No.	Population	F, %	Age, yrs	Hba1c, %	BMI	Wks	Intervention	n	No. of fractures	Comparator	n	No. of fractures
Iwamoto, 2010	NR	Japan	34	61 (10)	7.8 (0.9)	24.7 (3.5)	12	Sitagliptin (50mg)	163	0	Voglibose (0.2mg) TID	156	1 foot
NCT00707993	NCT00707993	Multi-country	55	70 (4.2)	NR	29.8 (4.4)	52	Alogliptin (25mg)	222	1 multiple 1 upper limb	Glipizide (5mg)	219	1 stress
NCT00856284	NCT00856284	Multi-country	50	55 (9.7)	7.6 (0.6)	31.2 (5.4)	104	Alogliptin (12.5mg, 25mg)	1765	3 ankle 1 femur 1 tibia 1 comminuted	Glipizide (5mg-20mg)/ Metformin (1500mg-3300mg)	874	1 ankle 1 facial bone 1 lower limb
NCT01006603	NCT01006603	Multi-country	38	73 (5.6)	NR	NR	52	Saxagliptin (5mg)	360	2 lumbar vertebra 1 femur 1 hand	Glimepiride (1mg-6mg)	360	1 ankle
Schernthaner, 2013	NCT01137812	Multi-country	44	57 (9.5)	8.1 (0.9)	31.6 (6.9)	52	Sitagliptin (100mg)	378	1 lower limb	Canagliflozin (300mg)/Metformin/ Sulfonylurea	377	1 hand 1 hip
Nauck, 2007	NCT00094770	Multi-country	41	57 (9.6)	7.7 (0.9)	31.3 (5.1)	52	Sitagliptin (100mg)	588	1 lower limb 1 radius 1 tibia	Glipizide (5mg-20mg)	584	1 ankle 1 lower limb 1 radius
Charbonnel, 2013	NCT01296412	Multi-country	45	57 (10)	8.2 (1)	32.7 (6)	26	Sitagliptin (100mg)	326	1 rib 1 spinal compression 1 sternal	Liraglutide (0.6mg-1.8mg)/ Metformin (>1500mg)	327	0
Arechavaleta, 2011	NCT00701090	Multi-country	46	56 (9.9)	7.5 (0.7)	30 (4.5)	30	Sitagliptin (100mg)	516	1 humerus 1 patella	Glimepiride (1mg-6mg)/ Metformin (>1500mg)	519	1 clavicle
Wainstein, 2012	NCT00532935	Multi-country	46	52 (11)	8.9 (1.3)	29.8 (5.8)	35	Sitagliptin (50mg) BID	261	1 femur	Pioglitazone (30mg-45mg)	256	0
Arjona Ferreira, 2013b	NCT00509236	Multisite	40	60 (9.5)	7.9 (0.7)	26.8 (5)	54	Sitagliptin (25mg)	64	1 hip 1 pelvic	Glipizide (2.5mg-20mg)	65	0
Aschner, 2010	NCT00449930	Multi-country	54	56 (11)	7.3 (0.7)	30.8 (4.8)	24	Sitagliptin (100mg)	528	1 tibia	Metformin (500mg-1000mg) BID	522	0
Goke, 2013	NCT00575588	Multi-country	48	58 (10)	7.5 (0.1)	31.4	104	Saxagliptin (5mg)	428	1 femoral neck 1 lumbar vertebra 1 patella 1 upper limb	Glipizide (5-20mg)/ Metformin	430	1 femur 1 humerus

Author, Year	Clinical trial No.	Population	F, %	Age, yrs	Hba1c, %	BMI	Wks	Intervention	n	No. of fractures	Comparator	n	No. of fractures
Study P049	NR	Multisite	54	56	7.2	NR	24	Sitagliptin (100mg)	455	1 tibia	Metformin (2000mg)	439	0
NCT00482729	NCT00482729	Multisite in US, Puerto Rico	43	50 (11)	9.9 (1.8)	NR	44	Sitagliptin (50mg) BID	625	1 rib	Metformin (500mg-1000mg) BID	621	1 rib, 1 skull

Abbreviation: F (female); Wks (duration in weeks); n (sample size); BMI (body mass index in Kg/m^2); HbA1c (glycated haemoglobin); TZD (thiazolidinedione); NR (not reported);
Mean (standard deviation) reported for age, HbA1c and BMI.
The patients had a mean age of 58 years, ranging from 49.7 to 72.6 years. There were 16 cases of fracture amongst 5,749 patients in the active comparator, and 31 fractures with 6,679 patients in the intervention group.